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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/812,238	03/29/2004	Kishore K. Wary	D6563	3362
7590	09/30/2005		EXAMINER	
Dr. Benjamin Adler ADLER & ASSOCIATES 8011 Candle Lane Houston, TX 77071			HADDAD, MAHER M	
			ART UNIT	PAPER NUMBER
			1644	

DATE MAILED: 09/30/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/812,238	WARY ET AL.
	Examiner) Maher M. Haddad	Art Unit 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 22 August 2005.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-41 is/are pending in the application.
4a) Of the above claim(s) 1-7, 12, 13, 18, 19, 22-31 and 34-41 is/are withdrawn from consideration.
5) Claim(s) _____ is/are allowed.
6) Claim(s) 8-11, 14-17, 20-21 and 32-33 is/are rejected.
7) Claim(s) _____ is/are objected to.
8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on 15 July 2004 is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____

4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .
5) Notice of Informal Patent Application (PTO-152)
6) Other: _____ .

DETAILED ACTION

1. Claims 1-41 are pending.
2. Applicant's election without traverse of Group II, claims 8-11, 1417, 20-21 and 32-33 drawn to a method of inhibiting cell-cell interaction, a method of treating a patient having a pathological condition and a method of inhibiting angiogenesis and the formation of capillaries in patient with antibody directed against a peptide comprises CRGDD sequence, angiogenesis and tumor growth as the species filed on 8/22/05, is acknowledged.

Upon reconsideration the examiner extended the search to cover inflammation.

While Applicant elected without traverse however, Applicant submits that the peptide of SEQ ID NO: 2 used in Group III was used to generate the antibody encompasses the sequence of peptide derived from VCIP of SEQ ID NO: 20 and 23 used to block the binding of the integrins.

Applicant concluded that the starting materials in Group II and Group III have a common core structure and hence are not distinct inventions. Applicant contends that a result prior art search for invention of Group II will also encompass invention of Group III and will not, therefore, pose a undue burden on the Examiner. Further applicant submits that the product of Group IV and IV be rejoined with the method of Group II on the ground that the invention does not teach or suggest the use of these antibodies or peptides in affinity purification, neither does the Examiner point out any reason or support for using these peptides in affinity purification. Applicant submits that the Examiner's assertion that the use of the products in affinity purification is not a reasonable use. Furthermore, Applicant submits that the products of Groups IV and VI are derived from the same core structure, i.e., RGD. This is not found persuasive because a method of using the specific antibody is a passive immunization while a method of using a specific peptide is an active immunization treatment. Therefore the methods of Group II and III are distinct. Regarding the product of Group IV (peptide) and VI (antibodies) are distinction because their structure and physiochemical properties are different. Further applicant statement that both the peptide and antibodies are derived from the same core structure of RGD sequence is unclear. While the Examiner acknowledge that the antibodies are made by immunizing an animal with the RGD core structure, however, the resultant antibodies would not have the core structure RGD, but rather the resultant antibody would bind to the core structure RGD containing peptide. Thus the Group IV and VI do not share a core structure as asserted by Applicant. Regarding the use of the peptide and the antibodies in affinity purification applicant contends this is "not a reasonable use." The Examiner is not clear as to why such a use is not a reasonable use since the affinity purification is a common technique wherein the peptide or the antibodies can be commonly use in the purification. Therefore the methods of inhibiting cell-cell interaction/angiogenesis with the specific antibodies/peptides are distinct and independent, and searches of all groups would place an undue burden upon the examiner due to the distinct and divergent subject matter of each Group. Further, a prior art search also requires a literature search. It is an undue burden for the examiner to search more than one invention.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 1-7, 12-13, 18-19, 22-31 and 34-41 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 8-11, 14-17, 20-21 and 32-33 are under examination as they read on to a method of inhibiting cell-cell interaction, a method of treating a patient having a pathological condition and a method of inhibiting angiogenesis and the formation of capillaries in patient with antibody directed against a peptide comprises CRGDD sequence, angiogenesis, inflammation and tumor growth as the species.

5. The specification is objected to under 37 CFR 1.821(d) for failing to provide a sequence identifier for each individual sequence. Figure 1L, IM and Fig14 H, on page 6 and page 13, respectively, have describe sequences that each must have a sequence identifier. Further the specification on page 34, table 1 has describe sequences that each must have a sequence identifier. Correction is required.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 8-9 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 8 is incomplete for omitting essential steps. While all of the technical details of a method need not be recited, the claims should include enough information to clearly and accurately describe the invention and how it is to be practiced. The minimum requirements for method steps minimally include a contacting step in which the reaction of the sample with the reagents necessary for the assay is recited. The instant claim is missing the step of contacting the cells with the reagents that block the binding of integrins to cell surface VCIP.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 8-11, 14-17, 20-21 and 32-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not provide enablement for a method of inhibiting cell-cell interaction, comprising the step of blocking the binding of "integrins to cell surface VCIP" in claim 8, wherein said cell-cell interaction is mediated by any "integrin ligand" in claim 9, wherein said binding is blocked by an antibody directed against any "peptide derived from VCIP", wherein said peptide "comprises" a CRGDD of SEQ ID NO: 41 in claim 10, wherein said peptide "has" the sequence of SEQ ID NO: 2 in claim 11, wherein the cell-cell interaction contributes to a biological process of "angiogenesis" in claim 14, or a method of treating a patient having a pathological condition resulted from integrin-mediated cell-cell interaction" said method comprises the step of administering to said patient any "agent" that blocks the binding of integrin to cell surface VCIP in claim 15, wherein said binding is blocked antibody directed against a "peptide derived from said VCIP" wherein said peptide "comprises" a CRGDD of SEQ ID NO:41 in claim 16, wherein said peptide "has" the sequence of SEQ ID NO: 2 in claim 17, wherein the cell-cell interaction contributes to a biological process of angiogenesis, wherein the pathological condition is tumor growth in claim 21, or a method of inhibiting angiogenesis and the formation of capillaries in a patient in need of such treatment, comprising the step of administering to said patient a pharmacological effective amount of antibody directed against any "peptide derived from VCIP, wherein said peptide "comprises" a RGD sequence in claim 32, wherein said peptide "has" the sequence of SEQ ID NO: 2 in claim 33. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte Forman*, 230 USPQ 546(BPAI 1986). They include the nature of the invention, the state of the art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are directed to methods of inhibiting cell-cell interaction/angiogenesis with any agent including antibodies directed against SEQ ID NO:41 or SEQ ID NO:2.

In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. No animal model system is used to inhibit cell-cell interaction or angiogenesis. Animal model studies in angiogenesis have not correlated well with in vivo clinical trial results in patients. Since the method of inhibiting indices of administering to the animal an anti-CRGDD antibody can be species- and model-dependent, it is not clear that reliance on the in vitro studies accurately reflects the relative human efficacy of the claimed therapeutic strategy. The specification does not adequately teach how to effectively inhibit angiogenesis or reach any therapeutic endpoint in humans by administering the anti-CRGDD antibodies. The specification does not teach how to extrapolate data obtained from in vitro studies to the development of effective in vivo mammalian including human therapeutic

treatment, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the anti-CRGDD antibodies exemplified in the specification.

There must be a rigorous correlation of pharmacological activity between the disclosed in vitro use and an in vivo use to establish practical use. The state of the art does not appear to recognize the antibody directed against SEQ ID NO: 41 or 2 would function in a method of inhibiting angiogenesis in tumor growth. In an article (The Scientist 16:33, 2002, Learning from Angiogenesis Trial Failures) Fogarty M writes that 12 recent failures of Phase III angiogenesis trial failures have bashed some scientists' hopes for success. Furthermore, in the same article Claude Hariton states that "multimodality is definitely the future in angiogenesis and antiangiogenic drug development because there is a dependency of several complex processes in angiogenesis. Shutting one door won't allow the drug to solve the problem. You have to shut, if possible, all the doors by which the vessels will grow around the tumor." Therefore, it is not clear that the skilled artisan could predict the efficacy of the anti-CRGDD antibodies exemplified in the specification. *In re Fisher*, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Further, Wallace (Drug Discovery Today, 3(10):433-4) teach that while there are ongoing clinical trials for the different categories of anti-angiogenic agents, we still have a limited understanding of the process of angiogenesis such that our ability to predict the efficacy of new agents is limited to the in vivo tumor growth animal models which often show promise in mice but are found ineffective in humans (page 433 column 2 in particular).

The current list of molecules identified as "antiangiogenic" is extensive, with significant diversity in their structural, chemical and biological properties (see Fan et al., Trends in Pharm. Sci. 16(2):57-66, page 57, column 2 and page 65, column 1, first paragraph in particular). Furthermore, because any treatment using any agent that blocks the binding of integrin via VCIP is not yet known and has not yet been disclosed, therefore, the method is only potential because it is not currently available in practical form. Therefore, the disclosure of mechanisms mediating cell-cell interaction does not provide sufficient guidance to a method of angiogenesis treatment in vivo.

The terms "has" and "comprises" in claims 10, 11, 16, 17, and 32-33 are open ended and extend the C/RGD/D peptides to include additional non-specified amino acids on either or both C-terminal or N-terminal of SEQ ID NOS: 42 or 2. Several publications implicated RGD in cell adhesion formation. The structural scaffold of the RGD motif is also indicated in a functionally optimal conformation. RGD motif and the amino acid sequence flanking the RGD play a role in the inhibition of angiogenesis. For example, the disintegrin kistrin (comprises the a cysteine consensus sequence) which have amino acids flanking the RGD sequence (PRGDMP), is potent inhibitors of platelet adhesion to fibrinogen but poor antagonist of the binding of platelets to immobilized fibronectin (Lu X et al (1994) Biochem J 304: 929-936). In contrast, elegantin which have markedly different amino acids around RGD (ARGDNP), preferentially inhibited platelet adhesion to fibronectin as opposed to fibrinogen and binds to an allosterically distinct

site on the α IIb β 3 complex. The claims encompass alterations in peptide's length because claims do permit deviation from the amino acid sequences of the consensus regions for a non-native protein. It would be reasonable to conclude that alterations in peptide's length would lead to a large alteration in binding affinity.

Further, the antibody that binds such epitope is unpredictable. For example, Colman *et al* in Research in Immunology (145(1):33-36, 1994) teach single amino acid changes in an antigen can effectively abolish antibody antigen binding. Abaza *et al* in Journal of Protein Chemistry (11(5):433-444, 1992) teach that single amino acid substitutions outside the antigenic site on a protein effect antibody binding. Further, Lederman *et al* in Molecular Immunology (28:1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document). Additionally, Li *et al* in PNAS (77:3211-3214, 1980) disclose that dissociation of immunoreactivity from other biological activities when constructing analogs (see entire document). There does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the various agents including antibodies recited in the instant claims. However, the specification fails to provide guidance as to how to determine specifically which other antibodies, specifically antibodies which bind the epitope "comprises"/"has" SEQ ID NO:41/2, would function in inhibiting cell-cell interaction including angiogenesis.

A person of skill in the art would not know which agents are essential, which agents are non-essential. There is insufficient guidance to direct a person of skill in the art to select particular agents as essential for inhibiting angiogenesis dependent VCIP. Without detailed direction as to which agents are essential to the function of the VCIP, a person of skill in the art would not be able to determine without undue experimentation which of the plethora of agents encompassed by the instant claims would share the ability to inhibit cell-cell interaction/angiogenesis mediated by VCIP.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

10. Claims 8-11, 14-17, 20-21 and 32-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of an in vitro method of inhibiting cell-cell interaction with the antibody that binds a peptide consisting of SEQ ID NO:2.

Applicant is not in possession of a method of inhibiting cell-cell interaction, comprising the step of blocking the binding of "integrins to cell surface VCIP" in claim 8, wherein said cell-cell interaction is mediated by any "integrin ligand" in claim 9, wherein said binding is blocked by an antibody directed against any "peptide derived from VCIP", wherein said peptide "comprises" a CRGDD of SEQ ID NO: 41 in claim 10, wherein said peptide "has" the sequence of SEQ ID NO: 2 in claim 11, wherein the cell-cell interaction contributes to a biological process of "angiogenesis" in claim 14, or a method of treating a patient having a pathological condition resulted from integrin-mediated cell-cell interaction" said method comprises the step of administering to said patient any "agent" that blocks the binding of integrin to cell surface VCIP in claim 15, wherein said binding is blocked antibody directed against a "peptide derived from said VCIP" wherein said peptide "comprises" a CRGDD of SEQ ID NO:41 in claim 16, wherein said peptide "has" the sequence of SEQ ID NO: 2 in claim 17, wherein the cell-cell interaction contributes to a biological process of angiogenesis, wherein the pathological condition is tumor growth in claim 21, or a method of inhibiting angiogenesis and the formation of capillaries in a patient in need of such treatment, comprising the step of administering to said patient a pharmacological effective amount of antibody directed against any "peptide derived from VCIP, wherein said peptide "comprises" a RGD sequence in claim 32, wherein said peptide "has" the sequence of SEQ ID NO: 2 in claim 33.

Neither the exemplary embodiments nor the specification's general method appears to describe structural features, in structural terms, that are common to the genus. That is, the specification provides neither a representative number of species (agents that blocks the binding for integrin to cell surface VCIP) to describe the claimed genus, nor does it provide a description of structural features that are common to species (agents that blocks the binding for integrin to cell surface VCIP). The specification provides no structural description of agents that blocks the binding for integrin to cell surface VCIP other than ones specifically exemplified; in essence, the specification simply directs those skilled in the art to go figure out for themselves what the claimed agents looks like. The specification's disclosure is inadequate to describe the claimed genus of agents.

Applicant has disclosed only amino acid of SEQ ID NO: 41 and 2; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 8-11 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Vassilev et al (Blood. 1999 Jun 1;93(11):3624-31), as is evidenced by Bendayan (J. Histochem. Cytochem. 1995, 43:881-886).

Vassilev *et al* teach a method of inhibiting platelet aggregation "cell-cell interaction" by anti-RGD antibodies (see page 3626, 1st col., 2nd paragraph and Fig. 4 in particular). Vassilev *et al* further teach that RGD motif has a central role in mediating cell-to-cell adhesion in a variety of immunological and inflammatory processes. For instance, cyclic RGD peptides have been shown to inhibit $\alpha 4\beta 1$ -dependent adhesion of T cells to cytokine-activated endothelial cells (see page 3629, 1st col., last paragraph to the 2nd col., 1st paragraph in particular). Further, antibodies "cross-react" with antigens with homologous amino acid residues. The reference anti-RGD antibody would bind to the peptide comprises SEQ ID NO: 41 and 2 due to the shared sequence homology. As is evidenced by Bendayan (J. Histochem. Cytochem. 1995, 43:881-886) who characterizes the specific reactivity of a monoclonal antibody produced to human proinsulin, and shows that although the antibody is highly specific, it is nevertheless able to bind to not only human proinsulin, but to proinsulin from other species and even a distinct protein, glucagons, based upon conservation of an Arg-Arg dipeptide sequence in each of these molecules (see entire document). Bendayan concludes that "an antibody directed against such a sequence, although still yielding specific labeling, could reveal different molecules not related to the original antigen" (page 886, last paragraph in particular).

While the prior art teachings may be silent as to the "blocking the binding of integrins to cell surface VCIP" per se; the method and the product used in the reference method are the same

as the claimed method. Therefore “blocking the binding of integrins to cell surface VCIP” is considered inherent properties.

Since the office does not have a laboratory to test the reference antibodies, it is applicant’s burden to show that the reference antibody does not bind to the SEQ ID NO:2 and 41 recited in the claims. See *In re Best*, 195 USPQ 430, 433 (CCPA 1977); *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and *In re Fitzgerald et al.*, 205 USPQ 594 (CCPA 1980).

The reference teachings anticipate the claimed invention.

13. Claims 15 and 20-21 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S Patent No. 5,807,819.

The ‘819 patent teaches a method of treating angiogenesis comprising administering to the subject RGD-containing peptides (agents) (see abstract and the entire document). The ‘819 patent further teaches that angiogenesis is required for the growth of solid tumors and neovascularization serves as a conduit for metastasis (see col. 9, lines 19-21 in particular).

While the prior art teachings may be silent as to the “blocks the binding of integrins to cell surface VCIP” per se; the method and the product used in the reference method are the same as the claimed method. Therefore “blocks the binding of integrins to cell surface VCIP” is considered inherent properties.

The reference teachings anticipate the claimed invention.

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 15-17 and 20-33 rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Pat. No. 5,807,819 in view of U.S. Pat. No. 5,567,440 and Vassilev et al, as is evidenced by Bendayan (J. Histochem. Cytochem. 1995, 43:881-886).

The teachings of '819 patent have been discussed, *supra*. Further, the '819 patent teaches methods of using the Arg--Gly--Asp containing peptides such as CRGDDVC (patented SEQ ID NO: 17) to alter $\alpha\beta 3$ integrin receptor-mediated binding of a cell endothelial cell to a matrix. The '819 patent teaches further teaches methods for ameliorating the severity of a pathology characterized by an undesirable level of angiogenesis in a subject using RGD-containing peptides (see the entire document including the abstract).

The claimed invention differs from the '819 patent teachings only by the recitation of antibody to SEQ ID NO: 2 or 41 in claims 16, 17 and 32-33.

The '440 patent teaches that cell adhesion plays an important role in human disease. These interactions proceed by the interaction of receptors upon the surface of a cell with proteins or glycosaminoglycans upon the surface of another cell or within the extracellular matrix. The '440 patent further teaches that routes to the interruption of these interactions typically involve competitive inhibition of these receptor-ligand interactions, for example, with antibodies, soluble ligands which act as receptor antagonists (e.g., cyclic RGD peptides), soluble receptors, or other competitors (see col., 1 lines 17-30 in particular).

Vassilev *et al* teach a method of inhibiting platelet aggregation "cell-cell interaction" by anti-RGD antibodies (see page 3626, 1st col., 2nd paragraph and Fig. 4 in particular). Vassilev *et al* further teach that RGD motif has a central role in mediating cell-to-cell adhesion in a variety of immunological and inflammatory processes. For instance, cyclic RGD peptides have been shown to inhibit $\alpha 4\beta 1$ -dependent adhesion of T cells to cytokine-activated endothelial cells (see page 3629, 1st col., last paragraph to the 2nd col., 1st paragraph in particular). Further, antibodies "cross-react" with antigens with homologous amino acid residues. The reference anti-RGD antibody would bind to the peptide comprises SEQ ID NO: 41 and 2 due to the shared sequence homology. As is evidenced by Bendayan (J. Histochem. Cytochem. 1995, 43:881-886) who characterizes the specific reactivity of a monoclonal antibody produced to human proinsulin, and shows that although the antibody is highly specific, it is nevertheless able to bind to not only human proinsulin, but to proinsulin from other species and even a distinct protein, glucagons, based upon conservation of an Arg-Arg dipeptide sequence in each of these molecules (see entire document). Bendayan concludes that "an antibody directed against such a sequence, although still yielding specific labeling, could reveal different molecules not related to the original antigen" (page 886, last paragraph in particular).

The limitation "blocks the binding of integrins to cell surface VCIP" would be expected properties of the resultant method.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the CRGDDVC cyclic peptide taught by the '819 patent with anti-RGD antibody taught by Vassilev *et al* in a method of inhibiting angiogenesis in a subject.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because routes to the interruption of cell-cell interactions typically involve competitive

inhibition of these receptor-ligand interactions with either receptor antagonists (e.g., cyclic RGD peptides), antibodies or other competitors.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

September 21, 2005

Maher Haddad

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